

Review Article

Treatment of Hypertension in Patients with Chronic Kidney Disease

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Abstract

Patients with hypertension and chronic kidney disease (CKD) younger than 80 years should have their blood pressure reduced to less than 140/90 mm Hg. Patients with hypertension and CKD aged 80 years and older should have their systolic blood pressure reduced to 140 to 150 mm Hg if tolerated. Patients with hypertension and CKD should be treated with either an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker but not with both drugs simultaneously. Controlled studies comparing stenting plus medical therapy versus medical therapy alone show that for the vast majority of patients with renal artery stenosis and either hypertension or CKD, management of renal artery stenosis should be limited to medical therapy. The Symplicity HTN-3 study showed in 535 patients with resistant hypertension that renal denervation was not better than a sham procedure in reducing the primary efficacy endpoint of change in office systolic blood pressure at 6 months and the secondary efficacy endpoint of change in means 24-hour ambulatory systolic blood pressure at 6 months.

Keywords: Hypertension; Chronic kidney disease; Antihypertensive therapy; Renal artery revascularization; Renal denervation

Divergence of Guidelines

In the absence of randomized control data, the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommended that patients with chronic kidney disease (CKD) should have their blood pressure decreased to less than 130/80 mm Hg [1]. In the absence of randomized control data, the National Kidney Foundation Kidney Disease Outcome Quality Initiative guidelines recommended that patients with CKD and hypertension should have their blood pressure decreased to less than 130/80 mm Hg [2]. In the absence of randomized control data, the American Heart Association 2007 guidelines recommended that patients with hypertension at high risk for coronary events including those with CKD should have their blood pressure decreased to less than 130/80 mm Hg [3].

A meta-analysis was performed of the 2,272 patients with hypertensive CKD without diabetes mellitus in the African American Study of Kidney Disease and Hypertension (AASK) [4], the Modification of Diet in Renal Disease (MDRD) [5], and the Ramipril Efficacy in Nephropathy 2 (REIN-2) [6] trials [7]. This meta-analysis demonstrated that a blood pressure of less than 125/75 to 130/80 mm Hg did not improve clinical outcomes more than a target blood pressure of less than 140/90 mm Hg [7]. Whether a blood pressure of less than 130/80 mm Hg benefits patients with proteinuria greater than 300 to 1,000 mg per day requires further study [7].

The American College of Cardiology Foundation/American Heart Association 2011 expert consensus document on hypertension in the elderly recommended that the blood pressure should be reduced to less than 140/90 mm Hg in adults younger than 80 years with CKD [8]. On the basis of data from the Hypertension in the

Very Elderly trial [9], these guidelines recommended that the systolic blood pressure should be reduced to 140 to 145 mm Hg if tolerated in adults aged 80 years and older [8].

The European Society of Hypertension/European Society of Cardiology 2013 guidelines for the treatment of hypertension recommend lowering the systolic blood pressure to less than 140 mm Hg in patients with diabetic or non-diabetic CKD [10]. In elderly patients with a systolic blood pressure of 160 mm Hg or higher, the systolic blood pressure should be lowered to 140-150 mm Hg [10]. A diastolic blood pressure target of less than 90 mm Hg is recommended in patients with CKD [10].

The 2012 International Society of Nephrology guidelines for treatment of blood pressure in patients with non-dialysis-dependent CKD recommend that adults with CKD without diabetes mellitus [11] or with diabetes mellitus [12] with hypertension and albuminuria less than 30 mg per 24 hours should have their blood pressure lowered to $\leq 140/\leq 90$ mm Hg with a class I B indication. If albuminuria greater than 30 mg per 24 hours is present, lowering of the blood pressure to $\leq 130/\leq 80$ mm Hg has a class II D indication which I would not follow [11,12].

The eighth report of the Joint National Committee for the management of high blood pressure in adults (JNC 8) recommended that patients with CKD younger and older than 60 years of age should have their blood pressure decreased to less than 140/90 mm Hg [13]. These guidelines also recommended that angiotensin-converting enzyme inhibitors or angiotensin receptor blockers should be used to treat hypertension in patients with CKD regardless of ethnic background either as first-line therapy or in addition to first-line therapy [13]. I concur with these recommendations. However,

angiotensin-converting enzyme inhibitors plus angiotensin receptor blockers should not be used simultaneously in the same patient [14-16].

In 651,749 US veterans, mean age 74 years, with CKD, patients with a systolic blood pressure of 130 to 159 mm Hg combined with a diastolic blood pressure of 70 to 89 mm Hg had the lowest adjusted mortality rates [17]. Patients in whom both systolic blood pressure and diastolic blood pressure were concomitantly very high or very low had the highest mortality rates [17].

Renal Arterial Stenosis

Although uncontrolled studies suggested that renal artery angioplasty or stenting in patients with renal artery stenosis with hypertension resulted in significant reductions in systolic blood pressure and stabilization of CKD, randomized, controlled trials of renal artery angioplasty have failed to show a benefit of this procedure in reducing blood pressure [18-20].

The Angioplasty and Stent for Renal Artery Lesions (ASTRAL) trial randomized 806 patients with atherosclerotic renovascular disease to renal artery revascularization plus medical therapy or to receive medical therapy alone [18]. At a median follow-up of 34 months, compared to medical therapy alone, the renal artery revascularization group had a similar systolic blood pressure, a smaller reduction in diastolic blood pressure, and similar rates of renal events [18]. In addition, serious complications associated with revascularization occurred in 23 patients, including 2 deaths and 3 amputations of toes or limbs [18].

Of 64 patients with atherosclerotic renal artery stenosis and a creatinine clearance less than 80 ml/min/1.73 m² randomized to stent placement plus medical therapy, 46 patients had the procedure, and 76 similar patients were randomized to medical therapy alone [19]. Stent placement did not affect progression of impaired renal function. In addition, the stent group had 2 procedure-related deaths, 1 late death due to an infected hematoma, and 1 patient who needed dialysis secondary to cholesterol embolism [19].

The Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) study randomized 947 patients with atherosclerotic renal artery stenosis and either systolic hypertension while taking 2 or more antihypertensive drugs or CKD to medical therapy plus renal artery stenting or to medical therapy alone [20]. At a median follow-up of 43 months, the rates of the primary composite endpoint of death from cardiovascular or renal causes, myocardial infarction, stroke, and hospitalization for congestive heart failure, progressive renal insufficiency, or the need for renal replacement therapy were similar for both groups [20]. There was no significant difference in the rates of the individual components of the primary endpoint or in all-cause mortality between both groups. However, the stent group had a 2.3 mm Hg lower systolic blood pressure than the medical therapy alone group ($p=0.03$) [20].

These studies show that for the vast majority of patients with renal artery stenosis and either hypertension or CKD, management of renal artery stenosis should be limited to medical therapy [21]. However, it remains to be seen if patients with severe stenosis to a single functioning kidney, severe stenosis and acute kidney injury,

and those presenting with flash pulmonary edema might benefit from stenting [21].

Renal Denervation

The European Society of Hypertension position paper summarized current evidence, unmet needs and practical recommendations on use of renal denervation to treat resistant hypertension in hypertension excellence centers [22]. The recently published Symplicity HTN-3 study was a prospective, single-blind randomized, sham-controlled trial which randomized 535 patients with resistant hypertension in a 2:1 ratio to undergo renal denervation or a sham procedure [23]. The primary efficacy endpoint of change in office systolic blood pressure at 6 months and the secondary efficacy endpoint of change in mean 24-hour ambulatory systolic blood pressure at 6 months were not significantly different between both groups. Fortunately, renal denervation therapy had not been approved by the United States Food and Drug Administration for treatment of resistant hypertension. This study is another example showing why appropriate controls are necessary in clinical studies to avoid a placebo effect.

On the basis of these data, I would not use renal denervation therapy to treat resistant hypertension at this time. Treatment of resistant hypertension in patients with CKD should be limited to intensive medical therapy at this time. Patients with hypertension and CKD younger than 80 years should have their blood pressure reduced to less than 140/90 mm Hg. Patients with hypertension and CKD aged 80 years and older should have their systolic blood pressure reduced to 140 to 150 mm Hg if tolerated. Patients with hypertension and CKD should be treated with either an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker but not with both drugs simultaneously.

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